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☐	L6	liposome adj10 (below adj5 transition)	44
☐	L5	DPPC adj10 (below adj5 transition)	3
☐	L4	DPPC adj10 (below adj3 transition)	3
☐	L3	DPPC adj5 (below adj3 transition)	3
☐	L2	(gel adj1 phase) adj5 load$	6
☐	L1	(gel$phase) adj5 load$	0

END OF SEARCH HISTORY

First Hit Fwd Refs Previous Doc Next Doc Go to Doc#
End of Result Set

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L3: Entry 3 of 3 File: USPT Oct 13, 1998

US-PAT-NO: 5820848
DOCUMENT-IDENTIFIER: US 5820848 A

TITLE: Methods of preparing interdigitation-fusion liposomes and gels which encapsulate a bioactive agent

DATE-ISSUED: October 13, 1998

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/9.4; 264/4.1, 424/1.21, 424/450, 424/9.321, 436/829, 516/102

CLAIMS:

What is claimed is:

1. A method of producing a pharmaceutical composition comprising an interdigitation-fusion liposome and a bioactive agent which comprises: (a) preparing sized liposomes having an average diameter of less than about 0.05 microns and comprising a symmetrical saturated phospholipid; (b) combining the sized liposomes with an amount of an inducer effective to induce fusion of the sized liposomes and interdigitation of the saturated phospholipid so as to form an interdigitation-fusion gel from the sized liposomes; (c) adding a bioactive agent to the gel; (d) incubating the interdigitation-fusion gel at a temperature above the transition temperature of the saturated phospholipid in the gel for a period of time effective to form an interdigitation-fusion liposome from the gel; and, (e) combining the interdigitation-fusion liposome and a pharmaceutically acceptable carrier, wherein the inducer is selected from the group consisting of short-chain alcohols, polyols, chaotropic salts and aqueous buffers and wherein the interdigitation-fusion liposome comprises the bioactive agent at an agent-to-lipid ratio (w/w) of at least about 2:1.

2. The method of claim 1 further comprising adding an additional lipid to the combination of liposomes and inducer prior to incubation.

3. The method of claim 2, wherein the additional lipid is a noninterdigitating lipid.

4. The method of claim 1, wherein the inducer is a short chain alcohol selected from the group consisting of methanol, ethanol, propanol and n-butanol.

5. The method of claim 4, wherein the inducer is ethanol.

6. The method of claim 5, wherein the effective amount of ethanol is an amount equal to about 5% of the weight of the lipid in the sized liposomes to about 20% of the weight of the lipid.

7. The method of claim 6, wherein the effective amount of ethanol is an amount equal to about 7% of the weight of the lipid in the sized liposomes.

8. A method of preparing a pharmaceutical composition comprising an interdigitation-fusion liposome and a bioactive agent which comprises: (a) preparing sized liposomes having an average diameter of less than about 0.05 microns and comprising a symmetrical saturated phospholipid; (b) subjecting the sized liposomes to a hydrostatic pressure of at least about 10,000 psi for a period of time sufficient to fuse the sized liposomes and interdigitate the saturated phospholipid, so as to form an interdigitation-fusion gel from the sized liposomes; (c) adding a bioactive agent to the gel; (c) incubating the interdigitation-fusion gel at a temperature above the transition temperature of the saturated phospholipid in the gel for a period of time effective to form an and, interdigitation-fusion liposome from the gel; (e) combining the liposome and a pharmaceutically acceptable carrier, wherein the interdigitation-fusion liposome comprises the bioactive agent.

9. The method of claim 8, wherein the amount of the hydrostatic pressure is at least about 20,000 psi.

10. The method of claim 9, wherein the amount of the hydrostatic pressure is at least about 40,000 psi.

11. The method of claim 8, wherein the amount of hydrostatic pressure is effective to sterilize the gel.

12. The method of claim 8, wherein the hydrostatic pressure is applied for a period of time of from about 1 minute to about 1 hour.

13. A method of producing a pharmaceutical composition comprising an interdigitation-fusion liposome and a bioactive agent which comprises: (a) preparing sized liposomes having an average diameter of less than about 0.05 microns and comprising a symmetrical saturated phospholipid; (b) incubating the sized liposomes for a period of time of from about 1 minute to about 1 hour, so as to form an interdigitation-fusion gel from the sized liposomes; (c) adding a bioactive agent to the gel; (d) incubating the interdigitation-fusion gel at a temperature above the transition temperature of the self-inducing lipid in the gel for a period of time effective to produce an interdigitation-fusion liposome from the gel; and, (e) combining the liposome and a pharmaceutically acceptable carrier, wherein the interdigitation-fusion liposome comprises the bioactive agent at an agent-to-lipid ratio (w/w) of at least about 2:1.

14. The method of claim 13, wherein the self-inducing lipid is di-O-hexadecyl phosphatidylcholine.

15. The method of claim 13, wherein the sized liposomes are incubated for from about 1 minute to about 1 hour.

16. The composition of claim 1, wherein the sized liposomes have an average diameter of about 0.025 microns, the saturated phospholipid is dipalmitoyl phosphatidylcholine, the inducer is ethanol and the amount of ethanol in the composition is from about 5% to about 20% by weight of the lipid.

17. The composition of claim 16, wherein amount of ethanol in the composition is about 17% by weight of the lipid.

18. The method of claim 1, wherein the symmetrical saturated phospholipid is selected from the group consisting of dimyristoyl phosphatidylcholine, distearoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, dimyristoyl phosphatidylserine, dipalmitoyl phosphatidylserine, distearoyl phosphatidylserine, dimyristoyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, distearoyl phosphatidylethanolamine, dimyristoyl phosphatidic acid, distearoyl phosphatidic acid, dipalmitoyl phosphatidic acid, dimyristoyl phosphatidylinositol, distearoyl phosphatidylinositol, dipalmitoyl phosphatidylinositol, hydrogenated soy phosphatidylcholine, dipalmitoyl phosphatidylglycerol, di-O-hexadecyl phosphatidylcholine, distearoyl phosphatidylglycerol and dimyristoyl phosphatidylglycerol.

19. The method of claim 8, wherein the symmetrical saturated phospholipid is selected from the group consisting of dimyristoyl phosphatidylcholine, distearoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, dimyristoyl phosphatidylserine, dipalmitoyl phosphatidylserine, distearoyl phosphatidylserine, dimyristoyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, distearoyl phosphatidylethanolamine, dimyristoyl phosphatidic acid, distearoyl phosphatidic acid, dipalmitoyl phosphatidic acid, dimyristoyl phosphatidylinositol, distearoyl phosphatidylinositol, dipalmitoyl phosphatidylinositol, hydrogenated soy phosphatidylcholine, dipalmitoyl phosphatidylglycerol, di-O-hexadecyl phosphatidylcholine, distearoyl phosphatidylglycerol and dimyristoyl phosphatidylglycerol.

Previous Doc Next Doc Go to Doc#

First Hit Fwd Refs Previous Doc Next Doc Go to Doc#
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L6: Entry 21 of 44 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756121 A
TITLE: Antibiotic formulation and use for drug resistant infections

Abstract Text (1):
A liposomal aminoglycoside formulation comprising a neutral lipid, a negatively charged lipids and a sterol. The formulation contains unilamellar vesicles having an average size below 100 nm. A process of making liposomes containing an aminoglycoside is provided where the hydration temperature is significantly below the transition temperature of the formulation. A method for the treatment of drug susceptible and drug resistant bacteria.

Detailed Description Text (5):
A lipid solution was prepared in methanol and chloroform as described in Example 1. A lipid powder was obtained in a spray drier (Yamato Pulvis Basic Unit, Model GB-21). The following settings were used: 1) pump dial at 3-4.5; 2) aspirator dial at 6; 3) pressure at 1.5 -2 Kgf/cm.sup.2 s; 4) inlet temperature at 50.degree. C.; and 5) outlet temperature at 40.degree. C. The spraying took place under nitrogen for two hours. The powder was collected and combined with amikacin drug solution (as prepared in Example 1). The resulting solution was mixed for 2 minutes using a high shear mixer (Virtishear)) at 1000 rpm. The solution was placed in a beaker and set in a 40.degree. C. water bath and hydrated with mixing until the solution reached 40.degree. C. (about 25 minutes). The solution was then placed in a homogenizer (Gaulin 15M) for approximately 30 passes at 10,000 psi while maintaining the inlet temperature at 40.degree. C. The resulting solution was filtered through a 0.8 micron nylon filter. The solution was ultrafiltered to replace unencapsulated drug with new buffer. The solution was washed with 7 to 10 volumes of buffer. The resulting product was heated to 40.degree. C. and filtered through successive 0.8, 0.45, and 0.22 micron (pore size) filters. Thus, a surprising aspect of the present invention is that the hydration of liposomes occurred significantly below the transition temperature of the formulation (about 52.degree. C.).

Previous Doc Next Doc Go to Doc#

L6: Entry 34 of 44 File: USPT Apr 25, 1989

DOCUMENT-IDENTIFIER: US 4825447 A
TITLE: Liposomal thermograph and methods for making and using same

CLAIMS:

14. A method for manufacturing a liposomal thermograph as in claim 11 further comprising the following additional steps:

Step (F): forming a second liposomes within a second liquid medium having a second pH and a second freezing point, the second liposomes having a second transition temperature within the second liquid medium, while simultaneously or subsequently

Step (G): loading the second liposomes with a second fluorescent dye, the fluorescent dye being confined to the lumen of the liposomes at a temperature below the transition temperature and above the freezing point of the second liquid medium, the fluorescent dye having at least one charge at the second pH, the fluorescent dye being amphiphilic, the fluorescent dye being self-quenchable, the fluorescent dye having a concentration within the lumen of the liposomes sufficient to be self-quenchable, while simultaneously,

Step (H): loading the first liposomes with a counterion having a charge opposite to the charge of the fluorescent dye at the second pH, the counterion confined to the lumen of the liposomes at temperature below the transition temperature and above the freezing point, and then

Step (I): enclosing the second liposomes into a second enclosure of the sachet.